012363

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

DATE: October 20, 1997

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: **CHLORPYRIFOS-METHYL** - Report of the Hazard Identification Assessment Review Committee.

FROM: Jess Rowland 10/20/97
Branch Senior Scientist,
Science Analysis Branch, Health Effects Division (7509C)

THROUGH: K. Clark Swentzel 10/20/97
Chairman, Hazard Identification Assessment Review Committee
Toxicology Branch II, Health Effects Division (7509C)

TO: Karen Whitby
Chief, Risk Characterization and Analysis Branch
Health Effects Division (7509C)

PC Code: 059102

BACKGROUND: On September 30, 1997, the Health Effects Division's Hazard Identification Review committee met to evaluate the toxicology data base of Chlorpyrifos-methyl to select toxicological endpoints for acute dietary as well as occupational and residential exposure risk assessments. The Committee also re-assessed the Reference Dose (RfD) established in 1986 for chronic dietary risk assessment and addressed the sensitivity of infants and children from exposure to Chlorpyrifos methyl as required by the Food Quality Protection Act of 1996. The Committee's decisions are summarized below.

CC: Rick Whiting, Science Analysis Branch
Caswell File
LAN storage

A. INTRODUCTION

The Health Effects Division's Hazard Identification Assessment Review Committee met to evaluate the toxicology data base of Chlorpyrifos-methyl to select toxicological endpoints for acute dietary as well as occupational and residential exposure risk assessments. The Committee also re-assessed the Reference Dose (RfD) established in 1986 for chronic dietary risk assessment and addressed the sensitivity of infants and children from exposure to Chlorpyrifos methyl as required by the Food Quality Protection Act of 1996.

B. FQPA CONSIDERATIONS

1. Neurotoxicity

- In an acute delayed neurotoxicity study, hens were given a single oral doses of Chlorpyrifos-methyl at 2500 or 5000 mg/kg. At 2500 mg/kg, the findings were equivocal since 1 of 10 hens exhibited vacuolated neurilemmal sheets and granular fragmented axons. At 5000 mg/kg, sciatic nerve histopathology was seen in 3 of 10 hens and positive vacuolation or demyelination and swollen fragmented axons in the spinal cord was seen in 4 of 10 hens (MRID Nos. 0099639, 00242153).

- In a subchronic delayed neurotoxicity study with chickens, Chlorpyrifos-methyl was administered at oral doses of 0, 5, 50 or 500 mg/kg/day for four weeks. No delayed neurotoxicity was seen; the NOEL was >500 mg/kg/day. For systemic toxicity, the NOEL was 50 mg/kg/day and the LOEL was 500 mg/kg/day based on decreased body weight and egg production (MRID No. 0072888).

- Data gaps exist for acute and subchronic neurotoxicity studies and thus cholinesterase inhibition FOB data as well as histopathology of the central and peripheral nervous systems are not available for evaluation after single or repeated exposures to Chlorpyrifos-methyl

2. Developmental Toxicity

- The developmental toxicity study in rabbits showed no evidence of additional sensitivity in young rabbits following pre- or postnatal exposure to Chlorpyrifos-methyl. Comparable NOELs were established for adults and offspring.

- The prenatal developmental toxicity study in rats, however, indicated increased sensitivity to the developing offspring following *in utero* exposure to Chlorpyrifos-methyl. Developmental toxicity was observed at a dose (50 mg/kg/day) that was not maternally toxic (Maternal NOEL = 100 mg/kg/day).

- In the developmental toxicity study, pregnant Sprague-Dawley *Spartan* rats received oral administration of Chlorpyrifos-methyl in corn oil at 0, 50, 100 or 200 mg/kg/day during gestation days 6 through 15. For maternal toxicity, the NOEL was 100 mg/kg/day and the LOEL was 200 mg/kg/day based on decreased body weight. For developmental toxicity, the LOEL was 50 mg/kg/day, the lowest dose tested, based on delayed ossification of sternebrae; a NOEL was not established. At 200 mg/kg/day, there was also an increase in the incidence of lumbar ribs or spurs (i.e., extra 14th ribs). The DER notes that the control incidence of these findings was low as compared to the historical incidence. Neither maternal nor fetal cholinesterase levels were measured in this study (MRID No.0099640).)

- In a prenatal developmental toxicity study conducted in Japan white rabbits (10/group), Chlorpyrifos-methyl was administered by gavage in corn oil at doses of 4, 8, or 16 mg/kg/day on gestation days 6-18. The maternal NOEL was 4 mg/kg/day, based upon 20% decreased food consumption during treatment at the maternal LOEL of 8 mg/kg/day and above, with posttreatment recovery The DER states that the developmental NOEL was 4 mg/kg/day, based upon a decreased number of corpora lutea, surviving fetuses and number of implantations at 8 mg/kg/day (the developmental LOEL) and above. However, since the decrease in number of corpora lutea is unlikely to be a treatment-related effect (because the does were not dosed prior to impregnation), the cesarean section and fetal data were reexamined. It was concluded that there did not appear to be any treatment-related effect on any fetal parameters. Therefore, the developmental NOEL was revised to $\geq$32 mg/kg/day. It was also noted the data included a dose range-finding study in rabbits, in which 8, 16, or 32 mg/kg/day was administered by gavage to rabbits for 14 days. Plasma ChE levels were measured at days 1 and 13 of the study, and were found to be decreased at 16 mg/kg/day and above by day 1. **The Committee recommended that the developmental NOEL and LOEL be revised and this information be reported adequately in the revised DER and 1-Liner data base** (MRID No. 0099640, 00242150).

3. Reproductive Toxicity

- In a three-generation reproduction study, Sprague-Dawley rats were fed diets containing Chlorpyrifos-methyl at 0,1 or 3 mg/kg/day for three successive generations. There was no increased sensitivity in pups over the adults. The parental/ systemic was LOEL was 1 mg/kg/day based on decreases in plasma and red blood cell cholinesterase activity; a NOEL was not established. For reproductive toxicity, the NOEL was 1 mg/kg/day and the LOEL was 3 mg/kg/day based on a slight decreases in the fertility index (MRID No. 0099640).

4. Cholinesterase Inhibition

- Data are not available to compare the effects of Chlorpyrifos-methyl on cholinesterase activity in the adults and pups since this endpoint was not evaluated either in the rat or rabbit developmental toxicity studies and was evaluated only in the adults (but not in the pups) in the three generation reproduction study in rats.

5. Developmental Neurotoxicity

- The Committee decided to place the requirement for a developmental neurotoxicity study in *reserve status* pending the results of the acute and subchronic neurotoxicity studies. Supporting evidence for the need for a developmental neurotoxicity is based on:1) the positive findings in the acute delayed neurotoxicity in hens; 2) the lack of NTE data; and 3)increased sensitivity in the developmental toxicity study in rats.

6.Susceptibility Issue: In the three-generation reproduction study in rats and the prenatal developmental toxicity study in rabbits, there was no indication of increased sensitivity of the young animals to pre-and/or postnatal exposure to Chlorpyrifos-methyl. However, in the prenatal developmental toxicity study in rats, developmental toxicity was observed at a dose (50 mg/kg/day) that was not maternally toxic (the maternal NOEL was 100 mg/kg/day), indicating a possible increased sensitivity in the developing offspring following *in utero* exposure.

III. HAZARD IDENTIFICATION

1. Acute Dietary (One-day)

A toxicological endpoint for acute dietary risk assessment was not selected due to the inadequate information available for a oral study in humans (MRID No. 0099639, 00242150). The Committee concluded that this study could be critical in the weight-of the evidence approach in selecting the toxicological endpoints for this exposure period. Neither the DER nor the one-liner data base provided adequate information. In the 1-liner data base reported "*daily oral doses of 0.1 mg/kg for 28 days without effect on blood chemistry hematology, urinalysis or plasma & RBC ChE.*" Therefore, the Committee recommended that this study be re-evaluated and a new DER prepared before selecting a toxicological endpoint for this risk assessment. The Committee noted that the re-evaluation of this study is critical because a human study with a similar dosing regimen was used for selecting the dose and endpoint selected for acute dietary risk assessment of the structurally-related chemical, Chlorpyrifos ethyl.

2. Chronic Dietary (RfD)

The RfD/Peer review Committee on 12/09/86, established a RfD of 0.01 mg/kg/day from the NOEL of 0.1 mg/kg/day and an Uncertainty Factor (UF) of 10. The LOEL was 1 mg/kg/day based on inhibition of plasma and red blood cell cholinesterase activity in dog observed in a two year study (MRID No. 0099642, 00242154).

Although the RfD report (12/09/86) indicated that an UF of 10 was used "for inter-and intr species variability", the report did not explain as to why ONLY a 10 x was applied inspite of using a NOEL from an animal study (i.e., conventionally a UF of 10 is used only in conjunction with a human study).

The Committee noted that the NOEL of 0.1 mg/kg/day observed in the dog study is identical to the "no effect" dose identified in the human study reference above and *"speculated"* that this may have contributed in the application of the 10 x factor for the RfD. Since this "speculation"could not be substantiated, **the Committee determined that the confirmation of the RfD should await re-evaluation of the human study.**

3. Occupational/Residential Exposure (Dermal/Inhalation)

The Committee determined that the DERs do not provide critical information necessary for selecting toxicological endpoints for occupational and residential risk assessments. Therefore, the Committee recommended re-evaluation of the following studies:

1. Human study; GH-RC27; (Oral)	0099639; 00242150
2. Human study; TMD-72-2(Inhalation)	0099640; 00242151
3. Human study; TMD-72-2 (Dermal)	0099640; 00242151
4. Rabbit study; 51-19-68/74; (Dermal)	0099639; 00242152
5. Rabbit study; TMD-72-2 (Dermal)	0099640; 00242151
6. Rat developmental toxicity study	0099640
7. Rabbit developmental toxicity study	0099640

IV. CONCLUSIONS

The Committee concluded that the data base shows sufficient evidence for enhanced sensitivity of infants and children for the following reasons:

(i) Demonstration of neuropathology in the acute delayed neurotoxicity study in hens at a dose lower than the LD50 in that species.

(ii) Demonstration of increased sensitivity to the developing offspring following *in utero* exposure in the prenatal developmental toxicity study in rats.

(iii) Structure activity relationship: Chlorpyrifos-methyl has a similar toxicity profile to Chlorpyrifos-ethyl, treatment with which has resulted in neuropathological lesions. Extensive testing of Chlorpyrifos-ethyl has also identified increased sensitivity of neonatal animals to pre- and/or postnatal exposure to the chemical, leading to the supposition that the same response tested might occur with Chlorpyrifos-methyl which has not yet been adequately.

(iv) Data gaps for acute and subchronic neurotoxicity study in rats; therefore cholinesterase inhibition and FOB data as well as histopathology of the central and peripheral nervous systems after single or repeated exposure to Chlorpyrifos-methyl are not available. Consequently, the need for a developmental neurotoxicity could not be assessed.

The Committee, however, determined that the determination of the UFs for the various exposure scenarios is not possible at this time because: 1) the issue of why only a 10 x was applied in deriving the RfD when a NOEL from an animal study was used has to be resolved (i.e., why a conventional UF of 100 was not used for inter-and intra species variation); 2) lack of critical information from pivotal studies that could influence toxicology endpoint selection; and 3) the impact both these factors will have on the determination of the UF's.

The Committee noted that although the 10 x for FQPA is required because of the demonstrated increased sensitivity, the application of the other conventional UF's will be depended on the following factors:

(i) If toxicology endpoint selection is from human studies for dietary and/or non-dietary exposure risk assessments, then the total UF would be 100 (10 x for inter-species variation and 10 x for FQPA).

(ii) If toxicology endpoint selection is from animal studies, then the total UF would be 1000 (10 x for inter-species variation, x 10 x for intra-species variation x 10 x for FQPA).

Therefore, the Committee concluded that this chemical should be reviewed again at a later date upon completion of the re-evaluation of the critical studies at which time a final determination will be made on the Uncetainty Factors for risk assessments for the dietary as well as non-deitary (occupational/residential) exposure senarios.

13544

002865

Chemical:	**Chlorpyrifos-methyl (ANSI)**
PC Code:	***059102***
HED File Code	**21100 HIARC**
Memo Date:	**10/20/1997**
File ID:	**TX012363**
Accession Number:	**412-01-0120**

HED Records Reference Center
02/09/2001